

*Original Research Article*

# Virological response to treatment with entecavir in a cohort of chronic hepatitis B patients from Saudi Arabia Preliminary result

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Abstract

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Entecavir is a potent first-line Hepatitis B Virus (HBV) drug. This study was conducted to study the efficacy of entecavir in the treatment of Chronic Hepatitis B (CHB) patients from Saudi Arabia. A retrospective cohort study of CHB patients who were treated with entecavir at the Al Badriyah Tower Hepatology Clinic, Jeddah. All included patients were planned to complete at least 48 weeks of treatment and HBV-DNA testing every 6 weeks. Patients who had additional cause for liver disease were excluded. We obtained demographic data (age, sex and nationality), and the patients were categorized as treatment-naïve or treatment-experienced. Hepatitis B e-antigen (HBeAg) status, baseline aspartate aminotransferase (AST), and HBV-DNA levels were determined for all of the patients. Patients were considered for treatment according to various treatment guidelines. We also assess the stage of hepatic fibrosis using the fibroscan. Entecavir was administered at a dose of 1 mg daily for lamivudine-experienced patients; the remaining patients received 0.5 mg daily. All patients were monitored for treatment compliance and treatment side effects during the follow-up. A total of 146 patients were enrolled. They were predominantly male (77, 53.4%), and the majority were Saudi (144, 98.6%). The mean age was 38.75 years (22-67). The mean serum AST level was 49.68 U/L (SD 52.7). Most of the participants were negative for e-antigen CHB (142, 97.3%), and 45 (30.8%) were treatment-experienced. Entecavir dose: A total of 109 (74.7%) patients received 0.5 mg entecavir, and 37 (25.3%) patients received 1 mg entecavir. The mean baseline HBV-DNA level was 4666174.1 (SD=20248231.6, range=2,269-110,000,000). The HBV-DNA levels determined after 24 and 48 weeks of treatment were significantly lower compared to the baseline levels (24 weeks: 1033602.5, SD=4068826.1; 48 weeks: 1721916, SD 5258661, P=.019 and .015, respectively). Fifty-nine patients completed 48 weeks of treatment or longer. Two patients were non-responders at 48 weeks, and two patients experienced viral breakthrough after initial drop. The longest duration of follow-up with sustained negative viremia was 144 weeks. Our data showed that entecavir is highly effective and safe long term treatment for CHB among Saudi patients

**Key words:** CHB, Entecavir, Lamivudine, Saudi Arabia, Treatment experiences, Treatment naïve

## INTRODUCTION

Chronic hepatitis B (CHB) is a leading global cause of Chronic Liver Disease (CLD) and Hepatocellular Carcinoma (HCC), and nearly 400 million people have been exposed to the hepatitis B virus (HBV) (Ott et al., 2012; Lavanchy, 2004; Lee, 1997). The main goal of treatment in CHB patients is to achieve sustained viral

suppression, thereby reducing the chance of progression to CLD and the development of HCC (European Association for the Study of the Liver, 2009; Liaw et al., 2012; Lok et al., 2007). During the last decade, several oral nucleoside and nucleotide analogs have been developed (European Association for the Study of the

Liver, 2009; Liaw et al., 2012; Lok and McMahon, 2007). Entecavir, a potent hepatitis B antiviral agent, has been shown to be an effective first-line HBV treatment and to be associated with a very low risk of resistance (Shepherd et al., 2009; Dimou et al., 2007; Ono et al., 2012). Entecavir is also one of the rescue oral treatments in HBV cases with lamivudine and multidrug resistance (Liaw et al., 2012; Kim et al., 2010; Petersen et al., 2012). Effective neonatal and early childhood HBV vaccination programs have been in place since the late 1980s in Saudi Arabia. However, Saudi Arabia is still intermediately endemic for HBV, and a large number of adults in this nation are infected with HBV (Madani, 2007; Fallatah and Akbar, 2010; Bajrai et al., 2014). Many of these patients are treatment candidates according to various treatment guidelines (European Association for the Study of the Liver, 2009; Liaw et al., 2012; Lok and McMahon, 2007; Abaalkhail et al., 2014); however, the treatment of CHB in Saudi Arabia can be challenging because most HBV-infected patients are in the immune-tolerant phase, with normal or near-normal aminotransferase levels. In addition, many of these patients are infected with the e-antigen-negative (HBeAg-negative) virus, which is more difficult to treat than e-antigen-positive HBV (Madani, 2007; Fallatah and Akbar, 2010; Abdo et al., 2012). Moreover, genotype D HBV, which is difficult to treat compared to other genotypes, is the most common HBV genotype in Saudi Arabia (Bajrai et al., 2014; Abdo et al., 2006).

Data on the treatment of CHB in Saudi Arabia with oral antivirals are very limited (Akbar, 2002; Saadah et al., 2012; Al-Ashqar et al., 2013). This study reports the outcome of treatment of 146 CHB patients with entecavir and the long-term follow-up for those completing 48 weeks of treatment or more. These patients were from the Al Badriyah Tower Hepatology Clinic in Jeddah, Saudi Arabia. The Al Badriyah Clinic treats and follows hepatitis patients in an outpatient setting.

## METHOD

This was a retrospective cohort study of CHB patients who were treated with entecavir at the Al Badriyah Tower Hepatology Clinic in Jeddah. The data collection was from March 2014 to December 2014.

Inclusion criteria: Patients with CHB confirmed by serological testing for hepatitis B surface antigen (HBsAg), HBeAg, and Hepatitis B e antibodies (HBeAb) as well as by HBV-DNA testing via polymerase chain reaction (PCR) were included in this study if they had treatment with entecavir starting 2012 or after. The participants were also required to agree to receive treatment with entecavir and to comply with the follow-up schedule for 48 weeks or more. We only included

patients who complied with the scheduled follow-up and underwent HBV-DNA testing every 6 weeks. Exclusion criteria: Patients with incomplete data, patients who had hepatitis B and C co-infection and patients who were receiving hepatotoxic medication or immunosuppressive treatments, such as methotrexate, were excluded.

For each patient, demographic data including age, sex, and nationality (either Saudi or non-Saudi) were obtained. Furthermore, the status of each patient was also determined as either treatment-naïve or treatment-experienced according to previous treatment with lamivudine or adefovir. HBeAg status (positive or negative) was determined for all patients. All of the patients underwent baseline testing to determine serum aspartate aminotransferase (AST) levels; the normal reference range used at the Al Badriyah lab is 15-37 U/L. The baseline HBV-DNA level was also determined. HBV-DNA testing was performed using PCR with the CobasAmpliPrep/CobasTaqMan HBV Test, v2.0 (Roche).

The indications for treatment included elevated HBV-DNA (>2,000 IU/mL) with or without elevated serum AST and alanine aminotransferase (ALT) levels and evidence of advanced liver fibrosis using the FibroScan (Echosens 2005 France) for staging. We included patients who had evidence of advanced fibrosis with a stage higher than F2 (7.2 kpa). This criterion was adopted based on previous studies and the information provided by the manufacturer (Marcellin et al., 2009; Friedrich-Rust et al., 2008).

Entecavir was administered at a dose of 0.5 mg for treatment-naïve patients and patients who underwent previous treatment with adefovir; it was administered at a dose of 1 mg for lamivudine-experienced patients (Dimou et al., 2007; Kim et al., 2010). A treatment response was defined as a  $\geq 1$ -log decrease in the level of HBV-DNA by PCR at 12 weeks, with undetectable HBV-DNA at 48 weeks; a partial response was defined as a decrease in HBV-DNA of  $\geq 1$  log but  $\leq 3$  log at 12 weeks, with at least a 3-log decrease in HBV DNA at 48 weeks; the absence of a primary response was defined as failure to achieve a 1-log decrease in HBV-DNA at 12 weeks; and viral breakthrough was defined as a 1-log increase in HBV-DNA after an initial drop during therapy (European Association for the Study of the Liver, 2009; Lok and McMahon, 2007; Abaalkhail et al., 2014).

## Statistical method

The SPSS version 22 was used for statistic, we obtained the descriptive statistic. We used the student T test to compare the difference of variables between male and females. We also used the T test to compare HBV-DNA drop at different intervals compared to the baseline.

**Table 1.** Demographic data for the 146 CHB patients

	Sex		Total	
	Male	Female		
Nationality	Saudi	77	67	144
	Non-Saudi	1	1	2
Total	78 (53.4%)	68 (46.6%)		146
Mean Age	39.95 SD 9.03	37.37 SD 9.71		P=0.186
HBeAg	Positive	74	66	140 (96%)
	Negative	4	2	6 (4%)
Decompensated cirrhosis	1	0		1 (.7%)
Treatment experience	23 /78	22/68		45 (30.8%)
Elevated serum AST	50	40		90 (61.6%)

**Table 2.** Laboratory results for the 146 patients who were included in the analysis

Test	Mean and SD	Normal range	Male	Female	P value
Serum AST U/L	49.68 (SD 52.7)	15-37	56.2	42.2	.08
HBV-DNA Baseline	4666174.1 SD 20248231.6 (110000000-2269)	Undetectable	6616373.1 SD 24579065.3	2429181.1 SD13545774.5	.014

**Table 3.** HBV PCR results of patients undergoing treatment at different follow-up points. The results are given as the mean difference from baseline HBV-DNA levels

	HBV-DNA at 6 weeks	HBV-DNA at 12 weeks	HBV-DNA at 24 weeks (only 8 patients)	HBV-DNA at 48 weeks (only 5 patients)
Mean difference from baseline HBV-DNA	799501.5 SD 3445308.2	800362.5 SD 3445757	1033602.5 SD 4068826.1	1721916. SD 5258661
P value compared to baseline	.007	.007	.019	.015

## RESULTS

A total of 146 patients were included according to the inclusion criteria. The patients were predominantly male, and the majority were Saudi (See Table 1 for demographic data). The mean age was 38.75 (22-67) years, SD=9.41. The male patients were older than the females, but this difference was not significant.

The mean serum AST level was 49.68 IU/L, SD=52.691.

### Patient characteristics

The majority of the patients were HBeAg-negative (Table 1). Only one patient had decompensated liver disease.

With respect to history of previous treatment, 45

(30.8%) patients had been treated with oral antiviral therapy, 37 (25.3) were previously treated with lamivudine, and 8 (5.5%) patients were previously treated with adefovir. The remaining 101 (69.2%) patients were treatment-naïve.

### Entecavir dose

The majority of the patients (109, 74.7%) received 0.5 mg entecavir. The remaining 37 (25.3%) patients received a dose of 1 mg because of previous lamivudine exposure.

### Laboratory results

The mean serum AST was higher than the normal upper

**Table 4.** Treatment durations of the patients enrolled in this study at the time of data analysis (in weeks)

Duration of treatment in weeks	Number of patients	Percent	Number of patients with detectable HBV-DNA at the time of last follow-up	Number of treatments experienced
6	3	2.1	0	0
12	9	6.2	1	5
18	32	21.9	1	4
24	43	29.5	*2	13
48	28	19.2	**3	7
72	16	11.0	0	4
96	9	6.2	0	2
144	6	4.1	0	2
Total	146	100.0	7	37

\*All of these patients were partial responders at 24 weeks, and all were lamivudine-experienced patients

\*\* One lamivudine-experienced patient and 2 patients with very high baseline viral loads

limit, as shown in Table 2. In addition, 90 (61.6%) patients showed elevated serum AST levels, and 28 of the 37 (75.6%) lamivudine-experienced patients had elevated serum AST levels. Furthermore, male patients tended to have higher serum AST levels (56.2 U/L) compared to female patients (42.2 U/L),  $P=0.08$ .

Patients who were HBeAg-positive had significantly higher HBV-DNA levels compared to HBeAg-negative patients (875,000,000 and 437,590.5, respectively;  $P<0.001$ ). HBV-DNA showed significant drop at 6, 12, 24 and 48 weeks table 3.

The mean duration of treatment was 40.8 weeks (SD 32, range= 6–144) table 4. The longest duration of follow-up with sustained negative viremia was 144 weeks for 4treatment-naïve and 2 lamivudine-experienced patients. These 6 patients showed a rapid initial drop in the level of HBV-DNA during the first 6 weeks of treatment and maintained undetectable HBV-DNA after week 48 table 4. In addition, three patients (one lamivudine-experienced patient and two treatment-naïve patients) continued to have positive HBV-DNA at 48 weeks. The two treatment-naïve patients had a very high baseline viral load and showed a 5-log decrease in HBV-DNA by 48 weeks, although the level was still detectable ( $<100$  IU/mL). Two of the patients who completed 48 and 72 weeks of follow-up had viral breakthroughs at 18 weeks then they resume the response; both of these patients were lamivudine-experienced. None of our patients reported entecavir-related side effects.

## DISCUSSION

Our results demonstrate that entecavir is effective for the treatment of CHB in Saudi patients, and about 97% of treatment-naïve patients who completed 48 weeks of

treatment or more achieved sustained viral suppression at 48 weeks. Similar results were shown in a previous study by Al Ashqar et al., which evaluated 43 patients treated with entecavir. The male-to-female ratio in this previous study was similar to that in our study, but the mean age was higher compared to that in our cohort. This difference in age might be due to the earlier age of diagnosis or earlier initiation of treatment in our cohort (Al-Ashqar et al., 2013). The majority (74.7%) of our patients was treatment-naïve, and the remaining patients were treatment-experienced. The rate of viral breakthrough in our study was lower compared to that reported by AlAsqar et al. (1.3% and 2.3%, respectively). This difference might be due to treatment non-compliance given that the response was resumed when the follow-up was extended to 48 weeks in one patient and 72 weeks in the other patient. Treatment non-compliance was previously recognized as a major factor for treatment failure or partial response (European Association for the Study of the Liver, 2009; Lok and McMahon, 2007). Because compliance is required to avoid drug resistance, the treating physician should stress its importance and closely monitor the compliance of CHB patients taking oral antivirals. Most of our patients were Saudis, and despite the decline in the prevalence of HBV in Saudi Arabia, a considerable proportion of the adult population is infected. Thus, a more precise determination of the age-specific prevalence of HBV in Saudi Arabia is warranted (Madani, 2007; Abdo et al., 2012). The majority of our patients were HBeAg-negative, and this result is similar to the findings of several other investigators from Saudi Arabia (Madani, 2007; Fallatah and Akbar, 2010; Abdo et al., 2006; Al-Ashqar et al., 2013). Oral antiviral therapy is also recommended by several CHB guidelines for the treatment of patients with decompensated cirrhosis, as it was shown to delay the

need for liver transplantation (European Association for the Study of the Liver, 2009; Ono et al., 2012; Shim et al., 2010). In our cohort, only one patient suffered from decompensated cirrhosis. This result might reflect a selection bias because our study was conducted in an outpatient setting, whereas all of our decompensated patients were treated in a hospital setting at King Abdulaziz University Hospital, Jeddah. The mean serum AST level was higher than the upper limit of normal according to our lab reference, although nearly 40% of our patients had normal baseline serum AST levels. Several previous studies have shown that normal serum AST and ALT do not rule out hepatic fibrosis, and some patients with normal enzyme levels might have significant or advanced fibrosis (Hu et al., 2008; Han and Kim, 2008; Lim et al., 2010).

In our cohort, entecavir was also effective in patients with previous lamivudine exposure. Several previous studies have shown that entecavir is effective in such cases at a dose of 1 mg. This dose was therefore used in the present study, as suggested by different CHB treatment guidelines (Liaw et al., 2012; Shepherd et al., 2009; Dimou et al., 2007; Kim et al., 2010; Sherman et al., 2006). In our cohort, the 3 patients with a partial or incomplete response at 48 weeks were lamivudine-experienced or had a very high baseline viral load. In such cases, the combination of tenofovir and entecavir might be the best treatment option, as this combination was shown to be effective in overcoming multidrug resistance in HBV (European Association for the Study of the Liver, 2009; Lok and McMahon, 2007; Petersen et al., 2012). Six of our patients maintained HBV suppression through 144 weeks of follow-up. These patients showed an initial drop in HBV-DNA levels that was greater than 3 log. Previous studies have shown that an early decrease in the HBV load to the nadir level with effective therapy decreased the likelihood of developing resistance, and the response was ultimately maintained (Buti et al., 2010). Several previous international studies have shown similar long-term outcomes, including more than 5 years of HBV suppression after entecavir treatment of CHB (Shepherd et al., 2009; Ono et al., 2012; Yuen et al., 2011). We did not test her for the result for HBV genotype in our cohort, the reason that our previous published data and other data on HBV genotype among Saudis is genotype D with no difference in clinical presentation or treatment response compared to other less recognized genotypes (Abdo et al., 2006; Fallatah et al., 2015).

We did not observe any side effects associated with entecavir treatment during the follow-up period in any of our patients. This result is consistent with the safety profile of entecavir that has been previously reported in several studies (European Association for the Study of the Liver, 2009; Lok and McMahon, 2007; Yuen et al., 2011; Seto et al., 2011).

## CONCLUSION

The study showed that entecavir was effective for the treatment of CHB in our cohort of treatment-naïve and treatment-experienced patients from Saudi Arabia. This study enrolled the largest cohort of CHB patients in Saudi Arabia to date. Close monitoring and serial HBV-DNA testing of lamivudine-experienced patients is warranted for the diagnosis of resistance to both lamivudine and entecavir.

## Limitations of the study

- 1- The retrospective nature of the data collection
- 2- Patients who had viral breakthrough or slow response did not had testing for resistant mutations in the center where the study was conducted, but they were advice to have it in another center and the result was not available for us at the time of reporting this data.
- 3- Large number of patients' longer duration of follow up is needed for the optimal response.

## Conflict of Interest

Neither author has a conflict of interest to declare in relation to this article.

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None

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